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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/765,026	01/13/1997	MARTINE BARKATS	ST94051-US	5544

7590 04/17/2002

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315

EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/765,026	BARKATS ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3./21/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-75,78,79,81 and 82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-75,78,79,81 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/21/02 has been entered.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47, 61-65, 67, 69-75, 78-79 and 81 are rejected under 35 USC 103(a) as being unpatentable over Yu et al. in view of Coyle et al. and Greenberger.

This rejection has been modified as a result of applicants' amendment filed 3/21/02.

Applicants claim a method for treating diseases such as ALS, Parkinson's disease (PD), hypertension, etc., wherein said diseases are characterized by an excess of free radicals, said method comprising administering to patients a replication defective adenovirus encoding an intracellular CuZn superoxide dismutase (SOD-1) operatively linked to a promoter enabling expression in a target cell.

Yu et al. (U.S. Patent 5,506,133, issued 4/9/96, filed 4/11/94, see whole document, particularly Column 2, lines 15-25; Column 6, lines 1-13 and Columns 9-10) recites that defective human CuZn SOD-1 has been linked to familial ALS and that expression of a SOD gene (SOD-4) which is structurally and functionally related to SOD-1 can be used to treat human diseases involving excess free radicals (i.e. diseases characterized by inflammation, etc.). Yu et al. discloses that adenoviral vectors can be used to express an SOD gene in target cells. Yu et al. does not teach the specifics of generating adenoviral vectors capable of expressing SOD-1 genes and does not provide a review of the roles of different SODs in reducing the levels of free radicals in humans.

Coyle et al. (Science, Vol. 262, 29 Oct. 1993, pp. 689-695, see whole article, particularly pp. 689-690 and 694) recites that the genes encoding SODs are known, recites the role(s) played by free radicals in diseases such as ALS, PD, etc., reviews the well known roles of the different forms of SODs in reducing the levels of free radicals, the role of increased levels of SOD-1 with protection of brain tissue from ischemic brain damage and the possible correlation between reduction or lose of CuZnSOD (SOD-1) activity with diseases such as ALS in humans.

Greenberger (U.S. Patent 5,599,712, See whole document, particularly Figs. 3a-3b, the paragraph bridging Columns 5-6, Columns 7-8, paragraph bridging Columns 11-12, Columns 13 and 16) teaches the specifics of the generation of replication defective adenoviral vectors capable of expressing human SODs (i.e. MnSOD or CuZnSOD (SOD-1), etc.) derived from genomic or cDNA sources) wherein the SOD gene is under control of a viral (i.e. the adenoviral MLP) promoter, human cells which are infected with said vectors and pharmaceutical compositions comprising said vectors. The vectors serve to reduce the level of free radicals in target cells.

The basic concept of the claimed invention is disclosed by Yu et al. in that Yu et al. discloses use of adenoviral vectors to deliver a human SOD gene to target tissues so as to alleviate disease conditions associated with excess free radicals. While Yu et al. does not recite use of the SOD-1 gene, the point of the Yu et al. invention is to express a gene (SOD-4) which is functionally and structurally related to SOD-1 so as to alleviate diseases associated with excess free radicals. The secondary references, Coyle et al. and Greenberger et al., simply provide teachings on the

specifics of generating adenoviral vectors (these procedures are well known in the art) and provide a review of the link between free radicals and diseases in humans.

The ordinary skilled artisan, seeking to treat diseases which are characterized by an excess of free radicals would have been motivated to combine the teachings of Yu et al. on the use of adenoviral vectors comprising a human SOD gene (SOD-4) structurally and functionally related to SOD-1 to target tissues so as to alleviate disease conditions which involve a defective SOD gene (such as SOD-1) and excess free radicals (i.e. diseases involving inflammation, oxidative stress, etc.) with the teachings of Coyle et al. on the role of SOD-1 in reducing excess free radicals in disease conditions such as PD and ALS and the possible correlation between reducing said levels of excess free radicals and alleviating disease conditions combined with the teachings of Greenberger on the generation of recombinant adenoviral vectors designed for the delivery of SODs (which can be SOD-1) to target cells wherein said adenoviral vectors are designed to reduce the levels of free radicals and thereby reduce the levels of cell damage due to said free radicals in order to generate adenoviral vectors to express the human SOD-1 gene in order to treat diseases characterized by an excess of free radicals. Additionally, one of ordinary skill in the art would have been motivated to express the SOD-1 gene in adenoviral vectors because defects in the human SOD-1 gene has been associated with a specific disease condition in humans (ALS) (See Yu et al. and Coyle et al.) and expression of the normal gene would be expected to alleviate this condition. Also, if expression of the SOD-4 gene as recited by Yu et al. could be expected to compensate for, or add to, SOD-1 expression in tissues (i.e. remove excess

free radicals), the ordinary skilled artisan would have been motivated to simply express the well known SOD-1 enzyme. It would have been obvious for the skilled artisan to use adenoviral vectors expressing SOD-1 to treat diseases associated with excess free radicals because all three references teach the relevance of SOD-1 to disease conditions in humans and because Yu et al. specifically teaches that adenoviral vectors (which can be made by the methods disclosed by Greenberger et al.) can be used to deliver an SOD gene functionally and structurally related to SOD-1 to target cells for the express purpose of alleviating diseases marked by defective levels of SODs and an excess of free radicals and because Coyle et al. indicates that an increase in SOD-1 expression reduction can reduce the levels of free radicals and possibly alleviate some human diseases characterized by excess free radical levels. Given the teachings of the cited prior art references and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 66 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. in view of Coyle et al., Greenberger and further in view of Engelhardt et al.

Yu et al. and Coyle et al. are cited as in the above 35 USC 103(a) rejection.

Greenberger (U.S. Patent 5,599,712), is cited as in the above 103(a) rejection. Greenberger does not recite the generation of adenoviral vectors containing non-functional E2, E4, etc. genes.

Engelhardt et al. (PNAS, Vol. 91, June 1994, pp. 6196-6200, see whole article, particularly the Abstract and last three paragraphs of the Discussion) teaches the use of adenoviral vectors containing a non-functional E2 gene. It is noted that PNAS Volume 91 was received in the U.S. Patent Office Biotechnology Library on June 27, 1994. Coyle et al. and Greenberger teach the basic aspects of the claimed invention absent the use of adenoviral vectors comprising inactivated or nonfunctional additional adenoviral genes such as the E2 gene. Since Engelhardt et al. teaches the desirability of using adenoviral vectors wherein the E2 gene is non-functional (i.e. said vectors result in improved transgene persistence and reduced inflammatory responses), it must be considered that the ordinary skilled artisan, seeking to generate an adenoviral vector for the expression of SOD, would have been motivated to use an adenoviral vector wherein the E2 gene is non-functional for the express, art recognized, desirability of using these vectors (i.e. generating an adenoviral vector construct desirable for use in gene therapy). It would have been obvious for the ordinary skilled artisan to use an adenoviral construct lacking a functional E2 gene because of the desirability (as disclosed by Engelhardt et al.) of using such a vector for gene therapy. Given the teachings of the cited prior art references and absent evidence to the contrary, it must be considered that the claimed invention would have been *prima facie* obvious to the ordinary skilled artisan and that said artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Coyle et al. in view of Greenberger and Le Gal La Salle et al.

Yu et al., Coyle et al. and Greenberger are applied as in the above 35 USC 103 rejections. Yu et al. Coyle et al. and Greenberger do not teach the use of the RSV-LTR promoter to drive expression of a heterologous gene in an adenovirus vector.

Le Gal La Salle et al. (Science, Vol. 259, 12 Feb. 1993, pp. 988-990, see whole article, particularly p. 988) recites the use of the RSV-LTR promoter in the context of driving expression of heterologous genes in recombinant adenoviruses.

Yu et al., Coyle et al. and Greenberger teach the essential aspects of the invention with the exception of using the RSV-LTR promoter to drive expression of the SOD gene. However, Le Gal La Salle et al. teach the use of the RSV-LTR promoter to drive expression of heterologous genes in a recombinant adenovirus expression vector. The ordinary skilled artisan, therefore, would have been motivated to use the RSV-LTR promoter for the express purpose of driving expression of the heterologous gene (i.e. the SOD gene) since Le Gal La Salle et al. specifically recites using the RSV-LTR promoter to drive expression of a heterologous gene in the context of a replication defective recombinant adenovirus vector. It would have been obvious for the ordinary skilled artisan to use this promoter because it is a well known promoter which has been used in the prior art (Le Gal La Salle et al.) to drive expression of heterologous genes in the context of a recombinant replication defective adenovirus vector. Given the teachings of the

cited prior art, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for this Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

David Guzo
April 15, 2002

DAVID GUZO
PRIMARY EXAMINER